Special Article

FIFTY YEARS LATER: THE SIGNIFICANCE OF THE NUREMBERG CODE

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THE Nuremberg Code is the most important document in the history of the ethics of medical research.[1-6] The Code was formulated 50 years ago, in August 1947, in Nuremberg, Germany, by American judges sitting in judgment of Nazi doctors accused of conducting murderous and torturous human experiments in the concentration camps (the so-called Doctors' Trial).[7] It served as a blueprint for today's principles that ensure the rights of subjects in medical research. Because of its link with the horrors of World War II and the use of prisoners in Nazi concentration camps for medical experimentation, debate continues today about the authority of the Code, its applicability to modern medical research, and even its authorship.[1,2,4,5,8] The chief prosecutor at the Doctors' Trial, General Telford Taylor, believed that one of the three U.S. judges, Harold Sebring, was the author of the Code.[2] Two American physicians who helped prosecute the Nazi doctors at Nuremberg, Leo Alexander and Andrew Ivy, have each been identified as the Code's author.[5,8-11] A careful reading

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THE NUREMBERG CODE

1. The voluntary consent of the human subject is absolutely essential.

   This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

   The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

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of the transcript of the Doctors' Trial, background documents, and the final judgment reveals that authorship was shared and that the famous 10 principles of the Code grew out of the trial itself.

In this article I will explain the important role that physicians had in the prosecution of the Nazi doctors and in the formulation of the Nuremberg Code and summarize how medical researchers have used the Code as a guide over the past five decades.

THE DOCTORS' TRIAL

The main trial at Nuremberg after World War II was conducted by the International Military Tribunal. The tribunal was made up of judges from the four allied powers (the United States, Britain, France, and the former Soviet Union) and was charged with trying Germany's major war criminals. After this first-of-its-kind international trial, the United States conducted 12 additional trials of representative Nazis from various sectors of the Third Reich, including law, finance, ministry, and manufacturing, before American Military Tribunals, also at Nuremberg. The first of these trials, the Doctors' Trial, involved 23 defendants, all but 3 of whom were physicians accused of murder and torture in the conduct of medical experiments on concentration-camp inmates.[7]

The indictment of the defendants was filed on October 25, 1946, 25 days after the conclusion of the first Nuremberg trial by the International Military Tribunal. The Doctors' Trial began on December 9, 1946, and ended on July 19, 1947. The case was heard by three judges and one alternate. Thirty-two prosecution witnesses and 53 defense witnesses, including the 23 defendants, testified. A total of 1471 documents were introduced into the record. Sixteen of the 23 defendants were found guilty; 7 of them were sentenced to death by hanging, 5 to life imprisonment, 2 to imprisonment for 25 years, 1 to imprisonment for 15 years, and 1 to imprisonment for 10 years. Seven were acquitted. The sentences were confirmed by the military governor, and, after the U.S. Supreme Court declined to review the case, the executions were carried out at the Landsberg prison.

For the United States and its chief prosecutor, Telford Taylor, the trial was a murder trial (and murder had been identified by the International Military Tribunal as a crime against humanity). Nonetheless, as Taylor pointed out in his opening statement, this was "no mere murder trial," because the defendants were physicians who had sworn to "do no harm" and to abide by the Hippocratic Oath.[12] He told the judges that the people of the world needed to know "with conspicuous clarity" the ideas and motives that moved these doctors "to treat their fellow human beings as less than beasts," and that "brought about such savageries" so that they could be "cut out and exposed before they become a spreading cancer in the breast of humanity."[12] One recurring theme was the relevance of Hippocratic ethics to human experimentation and whether Hippocratic moral ideals could be an exclusive guide to the ethics of research without risk to the human rights of subjects. In the trial's exploration of ideas that shaped medical-research ethics, three physicians had central roles: Leo Alexander, an American neuropsychiatrist, Werner Leibbrand, a German psychiatrist and medical historian, and Andrew Ivy, a renowned American physiologist.

Leo Alexander

Leo Alexander, a Viennese-born American physician, had joined the U.S. Army Medical Corps in 1942, before being stationed in England at the American Eighth Air Force base. At the end of the war, Alexander was sent on a special mission under the Combined Intelligence Objectives Sub-Committee, an intelligence organization with members from several nations, and charged by orders from Supreme Headquarters of Allied Expeditionary Forces to gather evidence for the Nuremberg trials. Two days before the opening of the Doctors' Trial, Alexander gave Taylor a memorandum entitled "Ethical and Non-Ethical Experimentation on Human Beings," in which he identified three ethical, legal, and scientific requirements for the conduct of human experimentation.[9] The first requirement established the right of the competent experimental subject to consent or refuse to participate in these terms: "the subject should be willing to undergo the experiment of his own free will. . . ." The second focused on the duty of physicians as expressed in the Hippocratic Oath, which Alexander restated in research terms: "the medical Hippocratic attitude prohibits an experiment if the foregone conclusion, probability or a priori reason to believe exists that death or disabling injury of the experimental subject will occur." The third characterized good research practices.

On April 15, 1947, Alexander gave Taylor a second memorandum.[9,11] In it he set forth in greater detail six specific conditions for ethically and legally permissible experiments on human beings. The first stated that

> the legally valid voluntary consent of the experimental subject is essential. This requires specifically the absence of duress, sufficient disclosure on the part of the experimenter and sufficient understanding on the part of the experimental subject of the exact nature and consequences of the experiment for which he volunteers, to permit an enlightened consent.

The five other conditions established the humanitarian nature and purpose of the experiment and the scientific integrity and obligations of the investigator to the welfare of the subject.

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Werner Leibbrand

On January 27, 1947, Werner Leibbrand, a German psychiatrist and medical historian at Erlangen University, opened the debate on medical ethics at Nuremberg.[12] He explained to the court that German physicians at the beginning of the 20th century had adopted a "biologic thinking" according to which a patient was a series of biologic events, and nothing more than "a mere object, like a mail package."[12] Leibbrand insisted that such a view precluded any human relation between physicians and their patients and that it represented a perversion of Hippocratic ethics and "a lack of morality and reverence for human life."[12] He strongly condemned physicians who conducted experiments on subjects without their consent, and testified that this was also the result of biologic thinking.

During cross-examination, defense lawyers asserted that "civilized" nations such as France, the Netherlands, Britain, and the United States had performed dangerous medical experiments on prisoners, often without their consent. They cited American malaria experiments[12-14] to argue that Nazi physicians had followed common research practices. Leibbrand replied that this American research also was wrong because "prisoners were in a forced situation and could not be volunteers."[12] Leibbrand insisted that "the morality of a physician is to hold back his natural research urge which may result in doing harm, in order to maintain his basic medical attitude that is laid down in the Oath of Hippocrates."[12] This strong accusation of American research by the prosecution's first medical-ethics witness created major unanticipated problems for the prosecution. It therefore became necessary to broaden the scope of the trial by defining the conditions under which risky human experimentation is ethically permissible.

Defense lawyers explained that Nazi doctors were ordered by the state to conduct such experiments as the high-altitude, hypothermia, and seawater experiments on inmates at the Dachau concentration camp to determine how best to protect and treat German fliers and soldiers. They contended that these experiments were necessary and that the "good of the state" takes precedence over that of the individual.[12] Leibbrand replied that "the state could order deadly experiments on human subjects, but the physicians remained responsible for [not] carrying them out."[12] Once these physiologic experiments became the centerpiece of the trial, reliance on psychiatrists alone was not possible. The prosecution needed a prestigious medical scientist who was an authority on research physiology and whose wartime scientific interests corresponded to those of the Nazi doctor defendants. This expert was Andrew Ivy.

Andrew Ivy

Andrew Ivy was an internationally known physiologist and a noted scientist. He also had first-hand knowledge of the Stateville Penitentiary experiments on malaria[12,13] in his home state of Illinois, which the Nazi defendants attempted to liken to those performed on concentration-camp inmates. When the secretary of war, through the surgeon general of the army, asked the board of trustees of the American Medical Association to nominate a medical advisor to the Nuremberg prosecution, Ivy emerged as the natural nominee. On June 12, 1947, Ivy came to Nuremberg for the third time, this time to testify in rebuttal for the prosecution. His testimony, the longest of the trial, lasted four days.[12]

In direct examination, Ivy presented to the judges three research principles that he had formulated at the request of the American Medical Association and which, he said, reflected common research practices.[12] His document entitled "Principles of Ethics Concerning Experimentation with Human Beings," adopted by the American Medical Association House of Delegates in December 1946, read in part:

> 1. Consent of the human subject must be obtained. All subjects have been volunteers in the absence of coercion in any form. Before volunteering, subjects have been informed of the hazards, if any. Small rewards in various forms have been provided as a rule.
> 2. The experiment to be performed must be based on the results of animal experimentation and on a knowledge of the natural history of the disease under study, and must be so designed that the anticipated results will justify the performance of the experiment. The experiment must be such as to yield results for the good of society, unprocurable by other methods of study, and must not be random and unnecessary in nature.
> 3. The experiment must be conducted only by scientifically qualified persons and so as to avoid all unnecessary physical and mental suffering and injury and only after the results of adequate animal experimentation have eliminated any *a priori* reason to believe that death or disabling injury will occur. . . .[15]

Ivy explained that these common-sense principles mirrored the understanding shared by everyone in practice in the medical community.[12] The first principle was that a physician would never do anything to a patient or subject before obtaining his or her consent. Ivy also asserted that, unlike Leibbrand, he did not consider prisoners to be in an inherently coercive situation and thus unable to give consent, because in democratic countries where the rights of individuals are respected, prisoners can always say yes or no without fear of being punished.[12] He testified:

> The American malaria experiments with 800 or more prisoners were absolutely justified, scientifically, legally and ethically even if they bring with them danger to human life. To treat malaria was an important scientific problem,

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and so long as the subjects volunteer and are explained the hazards of the experiments, there is no ethical reason against it. . . . If prisoners condemned to death are volunteers, then it was ethical to do just that.[12]

During cross-examination, Ivy acknowledged that there were no written principles of research in the United States or elsewhere before December 1946 and that the principles adopted by the American Medical Association were expressly formulated for the Doctors' Trial.[12] Ivy also recognized that the right of the research subject to withdraw from an experiment may not always exist, as in the malaria experiments in which the subjects had already been infected, or in dangerous experiments in which the subjects could be severely injured or fatally harmed. Ivy agreed with Leibbrand that researchers must refuse to conduct experiments on human beings when ordered by the state in order "to save lives," because in such cases subjects would not be volunteers. He declared that "[t]here is no justification in killing five people in order to save the lives of five hundred" and that "no state or politician under the sun could force [him] to perform a medical experiment which [he] thought was morally unjustified."[12] Ivy also stressed that the state may not assume the moral responsibility of physicians to their patients or research subjects, arguing that "[E]very physician should be acquainted with the Hippocratic Oath [which] represents the Golden Rule of the medical profession in the United States, and, to [his] knowledge, throughout the world."[12] When, finally, defense counsel asked Ivy to reconcile the Hippocratic moral maxim that forbids physicians to "administer a poison to anyone even when asked to do so" with conducting potentially lethal experimental interventions on volunteer subjects, Ivy replied, "I believe this Hippocratic commandment refers to the function of the physician as a therapist, not as an experimentalist, and what refers to the Hippocratic Oath is that he must have respect for life and the human rights of his experimental patient."[12]

MEDICAL ETHICS AND HUMAN RIGHTS

The judges at Nuremberg, although they realized the importance of Hippocratic ethics and the maxim *primum non nocere,* recognized that more was necessary to protect human research subjects. Accordingly, the judges articulated a sophisticated set of 10 research principles centered not on the physician but on the research subject. These principles, which we know as the Nuremberg Code, included a new, comprehensive, and absolute requirement of informed consent (principle 1), and a new right of the subject to withdraw from participation in an experiment (principle 9). The judges adopted much of the language proposed by Alexander and Ivy but were more emphatic about the necessity and attributes of the subject's consent and explicitly added the subject's right to withdraw.

In the traditional Hippocratic doctor–patient relationship, the patient is silent and dutifully obedient to the beneficent and trusted physician.[16-18] Obviously, the patient must seek the physician's help and initiate the therapeutic relationship with the physician.[17] But once patients agree to be treated, they trust that the physician will act in their interest, or at least will do no harm.[17,18] In research, which is outside the beneficent context of the physician–patient relationship, this trust may be misplaced, because the physician's primary goal is not to treat; rather, it is to test a scientific hypothesis by following a protocol, regardless of the patient-subject's best interest. It is therefore only through a conflation of treatment and research that Alexander and Ivy believed they could expand on Hippocratic ethics to protect the rights of subjects in human experimentation.[19,20] Their Hippocratic view of medical research may have prevented them from adequately appreciating the risks to research subjects, which are many times greater than the risks to patients who are merely being treated.[21] Hippocratic ethics, even when supplemented with informed consent, tend to submerge the subject's autonomy into what the physician-investigator thinks is best for the subject.

Informed consent, the core of the Nuremberg Code, has rightly been viewed as the protection of subjects' human rights. The key contribution of Nuremberg was to merge Hippocratic ethics and the protection of human rights into a single code. The Nuremberg Code not only requires that physician-researchers protect the best interests of their subjects (principles 2 through 8 and 10) but also proclaims that subjects can actively protect themselves as well (principles 1 and 9). Most strikingly, for example, in Hippocratic ethics the subject relies on the physician to determine when it is in the subject's best interest to end his or her participation in an experiment. In the Nuremberg Code, the judges gave the subject as much authority as the physician-researcher to end the experiment before its conclusion (principle 9).

50 YEARS AFTER NUREMBERG

The Nuremberg Code has not been officially adopted in its entirety as law by any nation or as ethics by any major medical association. Nonetheless, its influence on global human-rights law and medical ethics has been profound.[6] Its basic requirement of informed consent, for example, has been universally accepted and is articulated in international law in Article 7 of the United Nations International Covenant on Civil and Political Rights (1966).[6,22] Informed consent, with specific reliance on the Nuremberg Code, is also the basis of the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the most recent guidelines

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promulgated by the World Health Organization and the Council for International Organizations of Medical Sciences (1993).[23]

The World Medical Association, established during World War II, has been accused of purposely trying to undermine Nuremberg in order to distance physicians from Nazi medical crimes.[24] The election of a former Nazi physician and SS member, Hans-Joachim Sewering, to the presidency of that organization in 1992 added credibility to that accusation.[24] (Because of public criticism, Sewering later withdrew.) Nonetheless, the various versions of the Declaration of Helsinki promulgated by the World Medical Association since 1964, although attempting to have peer review supplement informed consent and even supplant it as their central principle in the context of "therapeutic research," all implicitly acknowledge Nuremberg's authority. Both the Nuremberg Code and the Declaration of Helsinki served as models for the current U.S. federal research regulations, which require not only the informed consent of the research subject (with proxy consent sometimes acceptable, as for young children), but also prior peer review of research protocols by a committee (the institutional review board of the hospital or research institution) that includes a representative of the community.[25]

The Nuremberg Code focuses on the human rights of research subjects, the Declaration of Helsinki focuses on the obligations of physician-investigators to research subjects, and the federal regulations emphasize the obligations of research institutions that receive federal funds. Nonetheless, by insisting that medical investigators alone cannot set the rules for the ethical conduct of research, even when guided by beneficence and Hippocratic ethics, and by adopting a human-rights perspective that acknowledges the centrality of informed consent and the right of the subject to withdraw, the Nuremberg Code has changed forever the way both physicians and the public view the proper conduct of medical research on human subjects. Fifty years after Nuremberg, we recognize the human-rights legacy of the Nuremberg Code and are better able to face the critical challenge of applying the Code in its entirety and enforcing its human-rights provisions.

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